REMARKS

The present application contains claims 1-88, the status of which is as follows:

(a) Claims 1-44, 57, 59-65, and 82-88 have been canceled without prejudice.

(b) Claim 45-56, 58, and 66-81 were previously presented.

No amendments have been made to the claims.

Claim Rejections Under 35 U.S.C. 103

The Examiner rejected all of the pending claims under 35 U.S.C. 103, over PCT Publication WO 99/63882 to Grinvald ("Grinvald '99") in view of US 5,477,858 to Norris ("Norris"), and, in the case of some claims, further in view of additional references.

Claim 45 of the present application recites "utilizing said at least one flow characteristic **for identifying** roughness on an inner wall of said at least one optically accessible blood vessel. (emphasis added)" (The other independent claims recite generally similar limitations.)

As stated by the Examiner, regarding Grinvald '99:

> However, they do not specifically disclose that their method includes the step of utilizing said at least one flow characteristic for identifying roughness on an inner wall of said at least one optically accessible blood vessel or that their invention includes a wall analyzer for utilizing said at least one flow characteristic for determining at least one property of an inner surface wall of said blood vessel.

The Examiner stated regarding Norris:

Norris et al. disclose an ultrasound imaging system for creating real-time images of tissue and blood flow (column 1, lines 18-21). They disclose that when plaque build up in vessels (i.e. causing roughness on an inner wall of vessel), the direction and speed of blood flow are altered (column 1, line 62-column 2, line 4). At the time if the invention, it would have been obvious to one of ordinary skill in the art to modify the invention of Grinvald et al. to have their computer serve as a wall analyzer to perform the step of utilizing at least one flow characteristic (i.e. flow direction, flow rate) for identifying roughness on an inner wall of said at least one optically accessible blood vessel, as Norris teaches that flow characteristics (i.e. flow direction, flow rate) are indicators of plaque formation (i.e. roughness on inner wall of blood vessel) (column 1, line 62-column 2, line 4).

The Applicant respectfully disagrees with the Examiner's assertion that it would be obvious to combine Grinvald '99 and Norris to arrive at the claims of the present application. The Applicant submits that **Norris does not teach that flow characteristics are used to detect the presence of plaque** (i.e., roughness on the blood vessel) wall, as recited in the independent claims of the present application. Rather, **Norris teaches that the presence of plaque on the blood vessel wall renders blood flow detection techniques, such as Doppler ultrasound imaging, inaccurate**. Thus, based on Norris, one skilled in the art would not conclude that the optical imaging techniques described in Grinvald '99 could be used to detect the presence of plaque on the blood vessel wall. Rather, based on Norris, one skilled in the art would conclude that the presence of plaque on the blood vessel wall would render inaccurate the optical imaging techniques described in Grinvald '99.

As stated by Norris "In the mid-1970's, ultrasound technology began to utilize the Doppler principle to obtain information on blood flow from moving scatterers in the blood." (Column 1, lines 40-42) In the portion of Norris cited by the Examiner (column 1, line 62 – column 2, line 4), Norris states the following regarding the use of Doppler ultrasound techniques to obtain information on blood flow (emphasis added):

> One of the problems with these techniques is that the peak frequencies which are proportional to blood flow velocities may be

inaccurate. **When plaque builds up in the vessels, the direction and speed of blood flow are altered.** The peak velocity at the sample site, as calculated parallel to the vessel, may have a direction different from the line of the vessel. **For the case where plaque is not symmetrical, the velocity component parallel to the wall is an inaccurate measure when measured using the assumption that flow is of peak velocity.**

In the above paragraph, Norris states that using Doppler imaging techniques to measure peak blood flow velocities **is inaccurate in areas of plaque** because the plaque alters the speed and the direction of the blood flow. **Norris does not teach that the Doppler imaging techniques are used to detect the presence of plaque.** The Background section of Norris, concludes by stating in the final paragraph:

> In summary, the contemporary evaluations of the vascular system are hampered by an inability to see all the influences on blood flow in a global fashion. X-ray angiography and tissue imaging provide a view of the vascular tree, but miss the details of flow within a vascular compartment and show none of the surrounding soft tissue. **Continuous wave Doppler ultrasound provides evidence of flow events, but tells <u>nothing</u> about the non-anatomical characteristics of the vessel and surrounding tissue** ...
>
> (Column 2, lines 24-32, emphasis added)

Thus, Norris teaches that using an imaging technique that images moving scatterers in blood in a blood vessel is <u>not</u> capable of providing information regarding the non-anatomical characteristics of the vessel and surrounding tissue (e.g., including plaque).

Norris describes the following in the "Disclosure of the Invention" section:

> An object of this invention is to provide an ultrasound imaging system capable of **producing gray scale images of the anatomy along with color images of blood flow** simultaneously in a single image....
>
> Another object of this invention is to provide an ultrasound imaging system which time shares between the processes of building the image and analyzing the velocity information intake to build an

image in close to real time **so that the image accurately depicts both tissue and blood flow.**

These and other objects of the invention are provided by an ultrasound blood flow/tissue imaging system for producing angiodynograms. Angiodynography contains some of the conventional elements of real-time ultrasonography and duplex imaging, such as echo-ranging, B-mode real-time displays, range-gating, and Doppler signal processing. New to this approach is the synchronization of all these signal processing events into a single real-time **image that shows not only the vascular anatomy and surrounding tissue but also the flow events within the vascular compartment.**

(Column 2, lines 41-64)

Thus, in the paragraphs quoted immediately above, Norris provides a solution to the problems associated with using Doppler imaging to measure blood flow in a blood vessel. The solution is to combine regular ultrasound images with Doppler images, in order to overcome the inaccuracies in the Doppler imaging. **Norris does not teach that the blood flow that is imaged using the Doppler imaging could itself be used to determine the shape of the blood vessel wall.**

As stated hereinabove, the Examiner stated regarding Grinvald '99:

However, they do not specifically disclose that their method includes the step of utilizing said at least one flow characteristic for identifying roughness on an inner wall of said at least one optically accessible blood vessel or that their invention includes a wall analyzer for utilizing said at least one flow characteristic for determining at least one property of an inner surface wall of said blood vessel.

Based on the sections of Norris quoted hereinabove, Norris teaches that using blood flow imaging (i.e., Doppler imaging) by itself is not sufficient for accurately imaging the vascular anatomy. Rather, Norris teaches that in order to image the vascular anatomy, regular ultrasound imaging is required, in addition to Doppler imaging. **Norris does not teach that flow characteristics, as determined by blood**

flow imaging (i.e., Doppler imaging), can be used to identify roughness on the wall of the blood vessel.

By contrast, the independent claims of the present application recite apparatus and methods for using blood flow imaging (i.e., optical images of moving erythrocytes) for identifying roughness (e.g., plaque) on the inner wall of a blood vessel. Optical imaging of the blood vessel is used to image individual erythrocytes, and/or cluster of erythrocytes. Actual flow paths of the erythrocytes or clusters are thereby mapped, and, on this basis, the presence of plaque on the blood vessel wall is determined.

As stated in the present application:

> [0067] In general, the above-described system is preferably used in order to detect blood flow patterns next to the walls of large blood vessels in the retina through reflection measurements through the walls of said vessels. The imaging optics arrangement 12 can then be a modified fundus camera. **The movement of individual red blood cells (RBC's) or conglomerates thereof in individual blood vessels is performed as described in detail in the above-referenced patent documents, preferably using pulses of green light flashed at rapid succession into the eye so as to obtain a "movie" of the movements of the RBCs in the retina.** ...
>
> [0069] **The flow patterns showing up along the walls of large vessels in the retina, such as those emerging from the optical disk, are analyzed, preferably to derive parameters or characteristics describing the deviation of the flow from low-curvature lines parallel to the axis of the blood vessel. From those parameters or characteristics, conclusions can be drawn about the roughness properties of the inner surface of the vessels,** preferably by comparison to experimentally derived values obtained in a model, by the evaluation of the curvature distributions of flux lines next to the vessel walls, or by using other parameters yielded by theoretical models derived from fluid dynamics.

The inventors of the present application discovered that using optical imaging techniques for imaging erythrocytes, generates images from which one is capable of deriving properties of the blood vessel wall. This is not obvious in view of Grinvald '99 and Norris. Grinvald teaches optically imaging moving erythrocytes within a blood vessel of a subject, but does not describe the use of the optical images to determine the presence of roughness. Norris teaches that the presence of plaque in a blood vessel generates inaccuracies in blood flow imaging (i.e., Doppler imaging), and, for that reason, blood flow imaging alone is not sufficient for determining the characteristics of the blood vessel wall. Based on the teachings of Norris, one skilled in the art would reason that using the optical imaging techniques described in Grinvald '99 one would not be able to determine properties of the blood vessel wall.

In view of the arguments provided herein, the Applicant submits that independent claims 45, 54, and 66 are patentable over Grinvald '99 in view of Norris. The remaining pending claims, being dependent from the aforementioned claims, and, therefore, of narrower scope than the aforementioned claims, are also patentable over the art of record.

The Applicant believes the amendments and remarks presented hereinabove to be fully responsive to all of the grounds of rejection and objection raised by the Examiner. In view of these amendments and remarks, the Applicant respectfully submits that all of the claims in the present application are now in order for allowance. Notice to this effect is respectfully requested.

Respectfully submitted,

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